REMARKS/ARGUMENTS

Claims 6-12, 14-23 and 25 are active. Claim 6 has been further limited by use of the transitional phrase "consisting essentially of" which limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention, see MPEP 2111.03. Claims 16 and 17 further describe allodynia or hyperalgesia associated with neuropathic pain as described on page 5, lines 9-11. Claim 25 which indicates that neuropathic pain is not associated with other types of chronic pain, finds support on page 2, lines 1 and 9. In view of the remarks above, no new matter is believed to have been added. Favorable consideration of these amendments and allowance of the case are respectfully requested.

Interview Summary Record

The Applicants thank Examiner Ramachandran for the courteous and helpful interview of December 14, 2010. The recent decision by the Board was reviewed and use of the transitional claim language "consisting essentially of" was proposed as a means for distinguishing the claimed methods from the prior art method of Smith, et al. which requires the administration of both a 5-HT3 and 5HT4 antagonist.

It was agreed that Omoigui's claims 12 and 80 did not specifically teach treatment of neuropathic pain with a serotonin receptor antagonist because claim 12 is only directed to a method of treating a "neuropathic pain syndrome" and does not single out a method using a serotonin receptor antagonist, while claim 80 was only to treatments using a serotonin antagonist, but does not single out treatment of neuropathic pain.

The alleged general motivation in Omoigui for treating all types of pain using serotonin receptor antagonists to reduce inflammation, which is deemed by Omoigui to be common to all types of pain, were reviewed. It was suggested that the Applicants consider a

selection argument (or submit additional data) showing the superior ability of compounds of formula (I) to treat neuropathic pain.

Rejection—35 U.S.C. §103(a)

Claims 6-12 and 14-23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Omoigui, et al., U.S. 2004/0038874, in view of Gaster et al., EP 0630376[1] and Smith et al., Neurosci. Lett. 271:61. These documents do not render the claimed invention obvious because they do not suggest or provide a reasonable expectation of success for treating **neuropathic pain** (associated with damaged nerve tissue) using a compound of formula (I).

Omoigui is relied upon for teaching "a method for treating persistent pain by inhibiting mediators of inflammation including serotonin", OA, lines 5-6 from bottom of page 3, for teaching that antagonism of inflammation will relieve all types of pain and for teaching that the "hallmarks of neuropathic pain are chronic allodynia and hyperalgesia", see the bottom of page 3 of the OA.

The Examiner acknowledges on page 4, lines 4-5 that "Omoigui do not teach the claimed compounds [of formula (I)] in a method of treating neuropathic pain". Thus, Omoigui do not disclose or suggest that neuropathic pain can be treated using a 5-HT4 serotonin receptor antagonist.

There is no disclosure in the art that neuropathic pain can be treated by administering a 4-HT4 serotonin receptor antagonist.

While Gaster was relied upon for disclosing compounds of formula I for treating irritable bowel syndrome, migraine, etc. Gaster does not disclose treatment of **neuropathic pain** using a serotonin 5-HT4 serotonin receptor antagonist. Gaster [0050] only describes treatment of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial

[1] Erroneously cited as EP 0630736 in the Official Action.

arrhythmias and stroke, anxiety and/or migraine with compounds of formula (I). Migraine is not a type of neuropathic pain. To further distinguish the invention, claims 17 and 18 further characterize allodynia and hyperalgesia associated with nerve damage and new claim 25 further refers to treatment of neuropathic pain that is not associated with non-neuropathic chronic pain, such as migraine. Thus, Gaster does not disclose or suggest use of these compounds for treating **neuropathic pain** associated with damaged nerves.

Smith is relied upon for teaching a method "comprising a combination administration of a 5-HT4 antagonist (SB 207266—not a compound of formula [1]) and a 5-HT3 antagonist which inhibited intestinal allodynia, see lines 11-13 on page 4 of the OA. Smith does not disclose that a 5-HT4 antagonist, per se, can treat pain, nor does it refer to neuropathic pain since intestinal allodynia as described by Smith is not neuropathic pain. Smith teaches that:

> 5-HT4 receptor antagonism potentiates inhibition of intestinal allodynia by 5-HT3 receptor antagonism.

Smith does not disclose that a 5-HT4 receptor antagonist would have any effect on intestinal allodynia in the absence of a 5-HT3 receptor antagonist. Smith teaches an animal model for nociceptive allodynia, not for neuropathic pain and the experimental data disclosed by Smith can not be correlated with **neuropathic pain** in any way. Indeed, a pain cannot be defined as neuropathic in the absence of a primary lesion or dysfunction in the nervous system and the test used by Smith did not involve any primary lesion or dysfunction in the nervous system (nerve damage). Therefore, the experimental data disclosed by Smith cannot be correlated with **neuropathic pain** in any way. Moreover, as amended the claims exclude the combined administration of a 5-HT4 and 5-HT3 antagonist due to use of the transitional phrase "consisting essentially of".

Furthermore, the scientific literature at the time of invention only teaches using 5-HT4 antagonists for treating non-neuropathic or nociceptive pain and would not have motivated one of ordinary skill in the art to select a compound of formula (I) to treat

neuropathic pain. This is shown by the attachments in Annex 1, 2, 3, 4, 5, 6 and 7 attached to this response.

Annex 1, *Wikipedia* "Serotonin receptor" clearly describes seven families of serotonin receptors, as well as a number of subtypes within some families, so that the number of serotonin receptors identified up to now amounts to almost twenty.

This information was available as of this application's filing date as the very same or similar classification was reported in Hoyer, et al., Pharmacol. Rev. 46:157-203 (Annex 2), Smith, et al., Curr. Pharm. Des. 1:363-372 (Annex 3) and Saxena, Pharm. Ther. 66:339-368 (Annex 4).

Wikipedia lists a number of serotonin receptor antagonists. The enclosed table (Annex 5) summarizes the therapeutic effects shown or proposed for these serotonin receptor antagonists. As shown there ***none*** of these antagonists was ever used or proposed for treating neuropathic pain. As a matter of fact, the therapeutic use of serotonin receptor antagonists at the time of invention was limited to the treatment of anxiety states, Alzheimer's disease, depression, schizophrenia, memory impairment, sleep disorders, substance abuse, migraine, nausea and vomiting, angina pectoris and hypertension, gastric motility disorders, and cardiac disorders.

Wikipedia lists only a pair of 5-HT4 serotonin receptor antagonists, namely L-lysine and piboserod. This latter antagonist corresponds to the compound of formula (I), where R is butyl. Piboserod is marketed under the trade name *Serlipet* for the management of atrial fibrillation and irritable bowel syndrome (IBS).

Please also refer to the very similar disclosure of Saxena (1995) where the therapeutic uses of drugs acting as serotonin receptor antagonists reported in Table 7 is limited to anxiety, migraine, depression, hypertension, psychosis, sleep disorders, feeding disorders, radiation vomiting, drug craving, schizophrenia, irritable bowel syndrome, memory

impairment, gastric motility and cardiac arrhythmias. Saxena lists only a pair of serotonin 5-HT4 receptor antagonists, GR125487 and SB207710. GR125487 is said to be useful for the treatment of IBS and SB2077190 for the treatment of cardiac arrhythmias. There is no disclosure or suggestion to use these compounds to treat neuropathic pain.

In addition, Gaster, et al., Medicinal Res. Rev. 17:163-214 (Annex 6) lists only one 5-HT4 serotonin receptor antagonists in clinical development, see page 192, first paragraph and Fig. 17 which is SB207710, trade name *Serlipet*. Gaster clearly discloses the potential therapeutic indications for 5-HT4 receptor antagonists and discloses four main categories of disorders, none of which are neuropathic pain: gastrointestinal, CNS, cardiovascular and urinary bladder.

As shown above the art at the time of invention did not disclose or suggest using a serotonin receptor antagonist, and even less a 5-HT4 serotonin receptor antagonist, to treat pain or even less neuropathic pain, which was then known to be a specific and peculiar type of pain associated with nerve damage that results in the sensation of pain and which differs from regular nociceptive pain.

Finally, the Applicants point out that there are only a few drug treatments for neuropathic pain and none of them involves the use of serotonin receptor antagonists, see *Wikipedia* "Neuropathic Pain" (Annex 7).

Consequently, none of the references alone teaches treatment of neuropathic pain using a compound of formula (I) and there is no suggestion to treat neuropathic pain using a compound of formula (I) in any of these references and thus one of ordinary skill in the art would not have been motivated to combine their teachings. Furthermore, none of these references provided a reasonable expectation of success for treating neuropathic pain by administering a compound of formula (I). As demonstrated above there was no suggestion in

the prior art to employ serotonin receptor antagonists, especially 5-HT4 receptor antagonists for treatment of neuropathic pain. Consequently, this rejection cannot be sustained.

Conclusion

In view of the amendments and remarks above, the Applicants respectfully submit that this application is now in condition for allowance. An early notice to that effect is earnestly solicited.

Respectfully submitted,

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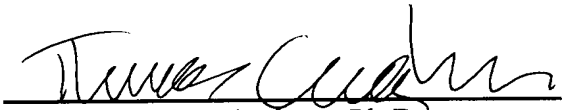

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